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GOVERNMENT & POLICY

January 7, 2002

Volume 80, Number 1
CENEAR 80 1 pp. 20-23
ISSN 0009-2347

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HEALTH AND SAFETY

WHAT'S HIDING IN TRANSGENIC FOODS?

Federal agencies seek allergenicity protocols to test and regulate genetically modified foods



BETTE HILEMAN, C&EN WASHINGTON

Over the years, as genetically engineered crops have been developed and marketed, critics have raised many objections. They fear the crops may cross with wild relatives and create superweeds, or the levels of toxins in the plants may turn out to be unexpectedly higher

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than those in conventional varieties, or insects may become resistant to the insecticides in the genetically modified plants.

But the potential drawback that has caused regulators and marketers the most consternation is the possibility that a novel protein--the protein coded by the transferred gene--in a genetically engineered plant may turn out to be a new allergen.

For example, Aventis' StarLink corn--genetically engineered to produce the insecticidal protein called Cry9C, which is derived from the soil bacterium *Bacillus thuringiensis*--was approved for animal or industrial, but not human, use because of the possibility that Cry9C may be an allergen. Because of this, after StarLink was discovered in some 300 corn products for people, mainly because of inadvertent commingling with non-StarLink corn, Aventis was forced to buy back all the StarLink from farmers and compensate food producers at an estimated cost of several hundred million dollars ([C&EN, Jan. 22, 2001, page 23](#)).

The [Environmental Protection Agency](#) has been unable to determine conclusively whether Cry9C is or is not an allergen. It finally decided there is a "medium likelihood" that Cry9C protein is an allergen, but a "low probability" that allergic responses would occur in populations exposed to the very low levels in the food supply. The main reason the agency had so much difficulty making decisions about StarLink was a lack of scientific knowledge about how to test for allergenicity, says Linda S. Birnbaum, director of the Human Studies Division at EPA's National Health & Environmental Effects Research Laboratory.

TO AVOID FUTURE StarLink-like imbroglios, and to preserve the advantages of growing genetically engineered crops, federal agencies are trying to work out an allergenicity testing protocol to use in regulating genetically engineered foods. To aid in this effort, EPA, the [National Institutes of Health](#), and the [Food & Drug Administration](#) held a conference on Dec. 10-12 in Chapel Hill, N.C. Among the problems discussed were how to tell if a protein is a potential allergen and what animal models might be used to screen products for possible human problems.

Attending the meeting were a wide variety of allergy experts, EPA and FDA regulators, and scientists from public interest groups. During the conference, they formulated a broad list of research projects that could help in developing a solid



Goldman

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testing protocol for allergenicity. In a few months, a report from the meeting will be sent to EPA, NIH, and FDA in the hope that they will fund research in the areas that could be most helpful in allergenicity testing, said Lynn R. Goldman, a professor of environmental science at [Johns Hopkins University Bloomberg School of Public Health](#) who was one of the conference organizers.

**Fu**

This was not the first conference to discuss the potential allergenicity of transgenic food. A year ago, the [United Nations Food & Agriculture Organization](#) and the [World Health Organization](#) jointly sponsored a meeting in Europe and worked out a decision tree for assessing whether a particular genetically modified food is likely to cause allergic reactions. But the decision tree is controversial, in part because the science behind several individual parameters in the scheme is not definitive.

**Buchanan**

It is easy to test for known allergens. For example, when a gene from the brazil nut was inserted into a soybean, a common test for known allergic reactions immediately showed that the brazil nut allergen had been transferred to the soybean, and the development of that particular transgenic soybean ceased.

**Bernstein**

PHOTOS BY
BETTE HILEMAN

But if the potential allergen is new, its allergenicity cannot be established or disproved with any standard test.

At the conference, [Dean D. Metcalfe](#), chief of the Laboratory of Allergic Diseases at the [National Institute of Allergy & Infectious Diseases](#), explained many of the unknowns about allergies that would apply to potential allergens from genetically engineered food. For example, most allergens are proteins, and two of the predictors of allergenicity are thought to be resistance to digestion and amino acid sequence homology with known allergens. But it is unclear how resistant to digestion a protein must be in order to be an allergen, and it is also unclear what degree of sequence similarity a potential allergen must have to a known allergen to raise concern, he said.

ANOTHER AREA in need of more research is mechanisms for cross-reacting allergens, Metcalfe said. For example, many people who are allergic to birch trees also become allergic to apples and pears. But there is no definitive way to screen for cross-reactivity.

Also, there are no well-developed animal models to use in allergenicity testing, Metcalfe claimed.

And finally, while some food allergens are allergen-specific immunoglobulin E (IgE) mediated--that is, they elicit IgE antibody responses--others are non-IgE mediated. Both of these mechanisms are poorly understood, especially non-IgE mediation, Metcalfe said. In addition, "we need to understand thresholds for sensitization to food allergens and thresholds for elicitation of a reaction with food allergens," he said.

Resistance to digestion is considered one of the characteristics shared by food allergens. However, this assumption may not apply to all of them, said Tong-Jen Fu, a research scientist at FDA. Her research has shown that a wide range of digestive stabilities are exhibited among food allergens. Also, digestion degradation products as small as 1 kilodalton--roughly eight amino acids--can be allergens, she said. "Allergens can be more stable or less stable than nonallergenic proteins in regard to digestion," she said.

PART OF THE PROBLEM with research on digestive stability of allergens is that the assay conditions have not been standardized, Fu said. Because of these inconsistencies, "research is needed to validate the notion that stability to digestion in the human gastrointestinal system is related to food allergy," she said.

Katherine Sarlo, principal scientist in the department of human and environmental services at [Procter & Gamble](#), explained that P&G has been experimenting with animals for years to test for allergic reactions to the enzymes it uses in its detergents. She suggested that a similar approach might be used to investigate potential allergic reactions to genetically engineered food.

In the 1960s when P&G first started using enzymes in detergents, many of its workers developed allergies to the enzymes, Sarlo said. In some plants, up to 50% of the workers had become sensitized to the enzymes, and a large proportion developed occupational asthma.

At this time, P&G began using certain strains of guinea pigs and mice to test the allergenicity of enzymes. The guinea pigs showed an immunoglobulin G (IgG) response to the enzymes that caused allergic reactions in some workers, and the mice showed both IgG and IgE responses to the enzymes. In choosing the strains of lab animal, P&G made sure the animals' responses to enzymes correlated with human responses, Sarlo said.

With a combination of lab animal research and medical surveillance of workers, P&G found that if it kept nominal levels of enzymes below 5 ng per m³, only 3% of the workers would become sensitized to the enzymes each year, and virtually none would exhibit allergic symptoms, Sarlo said. "The thresholds for sensitization are lower than the thresholds for symptomology. Now, a small

fraction of workers are still getting sensitized but are not exhibiting symptoms," she explained.

Bob B. Buchanan, professor of plant and microbial biology at the University of California, Berkeley, described his research on allergies in dogs. Dogs are a useful animal model for studying human allergens, he said, because dogs and humans share many characteristics. The set of substances that cause common allergic reactions in dogs is almost the same as the set of common human allergens, and the relative strength of individual allergens is the same in dogs as it is in humans. Also, allergy symptoms in dogs and humans are nearly identical, and the gastrointestinal systems of the two have many similar properties.

Buchanan has found that if the small protein thioredoxin is given to dogs allergic to milk, it reacts with a major milk allergen, b-lactoglobulin, and reduces vomiting and diarrhea.

In related work, he has introduced the thioredoxin gene into wheat in an attempt to make hypoallergenic wheat for dogs. The results of this research are not yet in. Buchanan's work may eventually have a double benefit. "It may be a good way to assess the allergic potential of genetically engineered foods, and it may help prevent allergies in dogs," he said. About 10 to 15% of dogs in the U.S. have allergies, most often to soy or corn.

Ricki M. Helm, an immunologist at Arkansas Children's Hospital Research Institute, said that swine have many advantages as an animal model for allergens. Like humans, swine develop the allergic symptoms, such as rhinitis, runny noses, and diarrhea, to food and environmental allergens. With skin tests, pigs show positive responses to allergen extracts. Also, their anatomy, physiology, and nutritional requirements are very similar to humans, and their immune systems mature in much the same way as human immune systems.

IN SWINE TESTS that Helm conducted for peanut allergy, piglets were sensitized to peanuts by giving them large doses soon after birth. Later they were exposed to high levels of peanuts, and many exhibited allergic symptoms, such as rashes and puffiness around the eyes. No animal was allowed to go into anaphylactic shock. The research on peanut allergies in swine may help in understanding and preventing peanut allergies in children, he said. It also shows that swine may be useful for testing the allergenic potential of transgenic food.

Speakers at the meeting disagreed about whether political leaders and the public would ever condone studies conducted on people to see whether they respond to potential food allergens. "Use of serum from people who have allergies may be the closest we ever get to human testing," said Steven M. Gendel, chief of FDA's Biotechnology Studies Branch.

But some participants said double-blind placebo-controlled food challenges (DBPCFCs) are the only way to determine conclusively whether an individual is reacting to a particular food. "I disagree with the idea that it is unethical to do DBPCFCs on people to possible allergens," said I. Leonard Bernstein, professor of clinical medicine at the University of Cincinnati College of Medicine. "Once you find a suspicious case, it is unethical not to do the challenges," he said, "because you can miss an allergy with a skin test." But DBPCFCs should not be used to screen the general population, he warned.

"Ultimately, we will have to rely on human studies to answer questions once and for all," said Robert G. Hamilton, director of the Johns Hopkins University Dermatology, Allergy & Clinical Immunology Reference Laboratory. "Limited clinical study of humans consuming approved genetically modified foods will be necessary," he said.

The meeting participants laid out a broad list of research projects that could help strengthen the regulation of transgenic food. Some of them are to identify and characterize known food allergens, develop clinically well-defined human serum banks to use in testing potential allergens, make available purified allergenic proteins for further development of animal models, and study how specific levels of IgE correlate with clinical disease. The conference proceedings and entire list of research needs will be published this year in *Environmental Health Perspectives*.

Val Giddings, vice president for food and agriculture at the Biotechnology Industry Organization, stressed that it may not be necessary to know the answers to all the research questions to ensure safety of transgenic food if the novel protein in the food is easily digested and not structurally similar to known allergens. "Some parties will say, 'These products should not be approved until you know all the answers,'" he said. But Giddings added that the lack of complete answers to all research issues should not prevent approval of all genetically engineered food products.

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ALLERGY MECHANISMS

Food Allergies: A Growing Problem In The U.S.

Experts agree that allergies in developed countries are becoming more common. But there isn't enough data to know whether food allergies are increasing, said Lynn R. Goldman, professor at the Johns Hopkins University Bloomberg School of Public Health, at a recent government-sponsored meeting in Chapel Hill, N.C., on assessing the allergenic potential of genetically modified foods.



Sampson

There is no question, however, that food allergies are a major problem. Studies show that, in the U.S., food allergies afflict 2 to 2.5% of adults and 6 to 8% of children, said Hugh A. Sampson, professor of pediatrics and biomedical sciences at the Mount Sinai School of Medicine. About 100 to 175 people in the U.S. die each year from food allergies, often to peanuts or tree nuts. The deaths generally follow anaphylactic shock.

Food allergies involve several types of immunological responses. The most common type is mediated by allergen-specific immunoglobulin E (IgE) antibodies. In this type of allergy, symptoms occur within minutes to a few hours after ingestion of the offending food.

Food allergies also include delayed hypersensitivity reactions. Here the mechanisms are less clear. Some of these are cell-mediated reactions involving sensitized lymphocytes in tissues rather than antibodies. In cell-mediated reactions, symptoms begin more than eight hours after ingestion of the allergenic food.

The most common allergenic foods associated with IgE-mediated reactions are peanuts, soybeans, milk, eggs, fish, crustacea, wheat, and tree nuts. More than 160 foods have been associated with allergic reactions.

Nearly all food allergens are proteins, which is why scientists are concerned that novel proteins coded by the transferred genes in genetically engineered foods will add to the burden of food allergies.

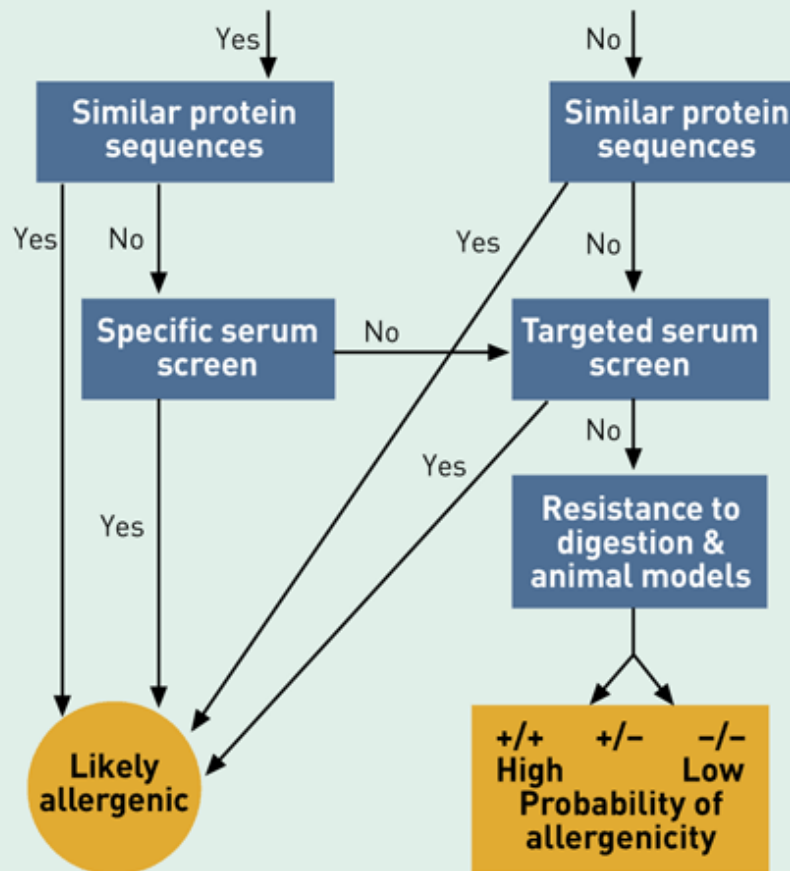
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DECISION TREE

Assessing allergic potential of transgenic foods

Is the source of the transferred gene allergenic?



At a joint meeting in January 2001, the Food & Agriculture Organization and the World Health Organization worked out a decision tree to assess the potential allergenicity of genetically engineered crops. The first question addressed in the scheme is: Is the source of the transferred gene a food that causes allergies? The next question is: Does the protein coded for by the transferred gene, or "novel protein," have a similar amino acid sequence to known food and environmental allergens? In the specific serum screen, the novel protein is tested using sera from people who are allergic to the source material for the transferred gene. In targeted serum screening, the novel protein is tested in pooled sera from people who are allergic to materials broadly related to the source material for the transferred gene. During the 2001 meeting, FAO/WHO acknowledged that the decision tree is not complete and would not apply to the evaluation of all foods. A similar decision tree is used

by industry to assess the potential allergenicity of transgenic foods it is developing, but FDA has not approved the scheme.

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